REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims fully supported by the specification and claims as originally filed, and do not add new matter. The specification has been amended to delete references to embedded hyperlinks and/or browser-executable code. Further, the paragraph starting on page 374, line 32 of the specification has been amended to comply with the provisions of the Budapest Treaty.

Prior to the present amendment, Claims 58-77 were pending in this application. With this amendment, Claims 71-73 have been canceled without prejudice, Claims 58-70 and 76-77 have been amended to further clarify what Applicants have always regarded as their invention, and new Claims 78-84 have been added. Support for the amendment of Claims 58-62 to recite "wherein the encoded polypeptide induces chondrocyte redifferentiation" can be found in Example 126 of the present application. Support for new Claims 78-84 can be found in the specification at, for example, page 129, line 25 to page 130, line 5, and page 108, lines 8-16.

Claims 58-70 and 74-84 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants thank the Examiner for entering the preliminary amendments of October 25, 2001, May 1, 2002 and August 28, 2002.

I. Specification

As requested by the PTO, Applicants have reviewed the application and deleted all references to embedded hyperlinks and/or browser-executable code. The ATCC address on page 372, line 34, has been amended and the paragraph beginning at page 374, line 32, has been amended to comply with the provisions of the Budapest Treaty. Additionally, the status of the prior US application 09/918,585 (now abandoned) has been updated.

The title of the present application has been amended to clearly indicate the invention to which the claims are directed.

II. Information Disclosure Statement

The Examiner has stated that the BLAST results cited in the Information Disclosure Statement submitted on March 25, 2002, have not been considered because the information on the referred databases is allegedly incomplete. Applicants file herewith an Information

Disclosure Statement listing each reference of the "BLAST Search" separately and including authors/inventors, database names, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

III. Priority

Applicants thank the Examiner for granting the priority date of the instant application as February 18, 2000.

IV. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 71-73 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite in view of the recitation of "nucleic acid that hybridizes" or "wherein said hybridization occurs under stringent conditions." The Examiner asserts that the intended hybridization conditions should be recited in the claims.

Without acquiescing to the Examiner's rejection, Applicants submit that the cancellation of Claims 71-73 renders the rejection of these claims moot.

Applicants further submit that newly added Claim 78 sets forth detailed hybridization conditions. Support for the hybridization conditions recited in Claim 78 may be found in the specification at, for example, page 129, line 35 to page 130, line 5. Thus the metes and bounds of Claim 78 and dependent Claims 79-84 are clear.

Accordingly, one skilled in the art would exactly know what the scope of the invention is, and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

V. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 58-62 and 74-77 are rejected under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description for the recited nucleic acids encoding variants of SEQ ID NO:59. The Examiner asserts that "the claims are drawn to a genus of molecules that is defined only by sequence identity." (Page 7 of the instant Office Action).

First, Applicants note that Figure 24 of the specification discloses the signal sequence of PRO363, comprising residues 1-16 of SEQ ID NO:59, as well as the transmembrane domain, comprising residues 232-251 of SEQ ID NO:59. As is known in the art, and defined in the specification, the extracellular domain of a protein is that region from the amino terminus to the

beginning of the transmembrane domain (see page 122, lines 12-14 of the specification). Thus the specification clearly describes the polypeptide of SEQ ID NO:59 lacking its associated signal peptide, the extracellular domain of the polypeptide of SEQ ID NO:59, and the extracellular domain of the polypeptide of SEQ ID NO:59, lacking its associated signal peptide.

Second, without acquiescing to the Examiner's position, Applicants submit that Claims 58-62, as amended herein, recite nucleic acids encoding amino acid sequences having at least 80% sequence identity to the polypeptide of SEQ ID NO:59, the polypeptide of SEQ ID NO:59 lacking its associated signal peptide, the extracellular domain of the polypeptide of SEQ ID NO:59, or the extracellular domain of the polypeptide of SEQ ID NO:59, lacking its associated signal peptide, wherein the encoded polypeptide induces chondrocyte re-differentiation. Example 126 of the present application (page 351, lines 18-32) provides the protocol for the chondrocyte re-differentiation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO363 polypeptide induces chondrocyte re-differentiation.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether an encoded variant PRO363 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward). Methods of isolating nucleic acid sequences encoding PRO polypeptides and polypeptide variants are described in the specification at, for example, page 185, lines 10-35; page 190, line 32, to page 191, line 8; and page 135, lines 7-21.

As noted by the Examiner, factors to be considered in evidencing possession of a claimed genus include "disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product,

or any combination thereof. (Page 7 of the instant Office Action). As discussed above, Applicants have recited structural features, namely, 80% sequence identity to the polypeptide of SEQ ID NO:59, which are common to the genus. Applicants have also provided guidance as to how to make the recited nucleic acids encoding variants of SEQ ID NO:59, including listings of exemplary and preferred sequence substitutions. The genus of claimed nucleic acids is further defined by having a specific functional activity for the encoded polypeptide, ability to induce chondrocyte re-differentiation. Accordingly, a description of the claimed genus has been achieved.

Withdrawal of the written description rejection of Claims 58-62 and 74-77 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

VI. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

Claims 58-62 and 74-77 are rejected under 35 U.S.C. §112, first paragraph, allegedly "because the specification, while being enabling for an isolated polynucleotide encoding the polypeptide of SEQ ID NO:59 and an isolated cell comprising said polynucleotide, does not reasonably provide enablement for a polynucleotide encoding a polypeptide not identical to SEQ ID NO:59 or a non-isolated cell comprising the polynucleotide." (Page 8 of the instant Office Action). The Examiner states that Claims 58-62 are directed to a genus of polynucleotides encoding polypeptides having at least 80% identity to SEQ ID NO:59 "wherein the polypeptides can have any function or no function at all." (Page 9 of the instant Office Action).

Without acquiescing to the Examiner's rejection, Applicants submit that Claims 58-62, as amended herein, recite nucleic acids encoding amino acid sequences having at least 80% sequence identity to the polypeptide of SEQ ID NO:59, wherein the encoded polypeptide induces chondrocyte re-differentiation. Thus the recited variant nucleic acids all encode polypeptides having the same function as the polypeptide of SEQ ID NO:59, and can be used in the same manner, for example, in the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis.

Example 126 of the present application (page 351, lines 18-32) provides the protocol for the chondrocyte re-differentiation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO363 polypeptide induces chondrocyte re-differentiation.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether an encoded variant PRO363 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward). Methods of isolating nucleic acid sequences encoding PRO polypeptides and polypeptide variants are described in the specification at, for example, page 185, lines 10-35; page 190, line 32, to page 191, line 8; and page 135, lines 7-21.

The Examiner has asserted that "[a]s taught by the art, a high degree of structural homology may not result in functional homology," and that therefore "the claimed genera of polynucleotides have the potentiality of encoding proteins of many different functions." (Page 9 of the instant Office Action). In support of this assertion, the Examiner cited articles by Witkowski *et al.* and Seffernick *et al.*

Witkowski *et al.* discloses that a single amino acid substitution transforms a beta-ketoacyl synthase into a malonyl decarboxylase. Applicants note that the authors made mutations at a known active site residue, and even so, of the various substitutions made, only one resulted in the gain of malonyl decarboxylase activity (Abstract). Further, this activity was one which the original enzyme was also capable of, although at a lower rate, and only under specific conditions (Abstract). Thus cases in which a single amino acid change results in altered protein function are clearly highly uncommon. Seffernick *et al.* disclose that two *Pseudomonas* enzymes having 98% sequence identity catalyze different reactions. The authors note, however, that "[i]n this superfamily and in others, members that catalyze different reactions are generally divergent to the extent that amino acid sequence identity is less than 50%" (page 2409, col. 1). The authors further note that "[t]he present finding that proteins with >98% sequence identity catalyze different reactions in different metabolic pathways is **highly exceptional**" (page 2409, col. 1; emphasis added). Thus Seffernick *et*

al. confirm that 80% amino acid sequence identity well within the level (of greater than 50%) for which protein function is expected to be conserved.

Further, there is no structural or functional similiarity between the PRO363 polypeptide and the proteins disclosed by Seffernick *et al.* and Witkowski *et al.* The PRO363 polypeptide is a transmembrane protein related to the cell surface viral receptor HCAR. Seffernick *et al.* and Witkowski *et al.*, in contrast, both studied soluble enzymes, in which targeted changes to a few key catalytic residues can alter protein function. In particular, the teachings of Seffernick *et al.* are directed to bacterial enzymes, which undergo unique selection pressures (page 2409, col. 2). Thus there is no basis for extrapolating the results obtained with these structurally and functionally completely different proteins to the predictability of the effect of mutations on the PRO363 polypeptide.

Accordingly, one of ordinary skill in the art would be able to use the guidance provided in the specification, including the listing of conservative amino acid substitutions provided in Table 6, to make nucleic acids encoding variants of SEQ ID NO:59 that would be expected to retain the activity of SEQ ID NO:59 in inducing chondrocyte redifferentiation.

Applicants further note that the claims are not directed to all possible variants having at least 80% amino acid sequence identity to SEQ ID NO:59, but only to those variants which retain the ability of the polypeptide to induce chondrocyte redifferentiation. The specification provides the protocol for a chondrocyte redifferentiation assay, as disclosed in Example 126. It would be a simple matter for one skilled in the art to test the encoded polypeptides to see if they induce chondrocyte redifferentiation using the methods of Example 126. This would not require undue experimentation.

The claims recite nucleic acids encoding polypeptide sequences associated with a biological activity. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed nucleic acid sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be

complex does not necessarily make it undue, if the art typically engages in such experimentation."[1]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of nucleic acids encoding polypeptides having at least 80% identity to SEQ ID NO:59 wherein the polypeptide induces chondrocyte redifferentiation can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

The Examiner further asserts that "the recited structural features as interpreted, such as "any fragment of the polypeptide of SEQ ID NO:59" or "any fragment of the polypeptide of SEQ ID NO:59 lacking its signal sequence", do not constitute a substantial portion of the genus," and that therefore "one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the invention was filed." (Page 10 of the instant Office Action).

First, this point appears to concern the issue of written description, not enablement. Second, Applicants respectfully submit that the claims do not recite "any fragment of the polypeptide of SEQ ID NO:59" or "any fragment of the polypeptide of SEQ ID NO:59 lacking its signal sequence." Rather, the claims recite a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO:59, or a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO:59, lacking its associated signal peptide. Figure 24 of the specification discloses the signal sequence of PRO363, comprising residues 1-16 of SEQ ID NO:59, as well as the transmembrane domain, comprising residues 232-251 of SEQ ID NO:59. As is known in the art, and defined in the specification, the extracellular domain of a protein is that region from the amino terminus to the beginning of the transmembrane domain (see page 122, lines 12-14 of the specification). Thus the specification clearly describes the polypeptide of SEQ ID NO:59 lacking its associated signal peptide, the extracellular domain of the polypeptide of SEQ ID NO:59, and the extracellular domain of the polypeptide of SEQ ID NO:59, lacking its associated signal peptide.

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[1] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

Applicants respectfully submit that it is well known in the art that the signal peptide of a protein is not required for function, but serves as a signal for import of the protein into the cell membrane. Once the protein is transported, the signal peptide is cleaved to produce the mature protein. Thus one of ordinary skill in the art would understand that the recited polypeptide of SEQ ID NO:59 lacking its associated signal peptide would have the same activity as the full length SEQ ID NO:59. Accordingly, one of ordinary skill in the art would understand how to use the claimed nucleic acids encoding the polypeptide of SEQ ID NO:59 lacking its associated signal peptide, without any undue experimentation.

Further, it is well known in the art that proteins involved in cell signaling, such as proteins that induce chondrocyte redifferentiation, mediate their effects via their extracellular domains, which are positioned to interact with other cells. Accordingly, one of ordinary skill in the art would expect the recited extracellular domain of SEQ ID NO:59, with or without the signal peptide sequence, to share the same chondrocyte redifferentiation activity of the full length SEQ ID NO:59. In addition, the specification discloses that PRO363 has homology to the cell surface protein HCAR, a membrane-bound protein that acts as a receptor for subgroup C of the adenoviruses and subgroup B of the coxsackieviruses (page 4, lines 19-30). The specification further discloses that "extracellular domains derived from the PRO363 polypeptides may be employed therapeutically *in vivo* for lessening the effects of viral infection" (page 199, lines 37-38). Accordingly, one of ordinary skill in the art would understand how to use the claimed nucleic acids encoding extracellular domains of PRO363, without any undue experimentation.

Finally, the Examiner asserts that Claim 76 is allegedly lacking enablement because the claim is not limited to "an isolated host cell." (Page 10 of the instant Office Action).

Without acquiescing to the Examiner's rejection, Claims 76 and 77 have been amended to recite an "isolated" host cell. Thus this aspect of the rejection is moot.

Accordingly, withdrawal of the enablement rejection of Claims 58-62 and 74-77 under 35 U.S.C. §112, first paragraph, is respectfully requested.

VII. Claim Rejections Under 35 U.S.C. §102

Claims 58-64, 66 and 68-77 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Holtzman *et al.*, U.S. 2002/0055139 A1, with priority to May 14, 1999. Holtzman *et al.* discloses an isolated nucleic acid that encodes a polypeptide, human A236 protein, that is 100% identical to SEQ ID NO:59, as well as expression vectors and host cells comprising the nucleic acid. Applicants respectfully point out although the Office Action states that Holtzman *et al.* has priority to "at least" May 14, 1999, none of the earlier applications to which U.S. 2002/0055139 claims priority appear to disclose the human A236 protein. Accordingly, May 14, 1999 is the earliest effective priority date for the disclosure of the human A236 protein by Holtzman *et al.*

Applicants submit that the cancellation of Claims 71-73 renders the rejection of these claims moot.

Applicants respectfully submit a Declaration under 37 C.F.R. §1.131 by Dr. Desnoyers, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood that establishes that Applicants had cloned and sequenced SEQ ID NO:58, and determined the homology of the encoded polypeptide (SEQ ID NO:59) to the cell surface protein HCAR, before the prior art date of May 14, 1999. The consideration of the Declaration is respectfully requested.

Applicants respectfully submit that an executed copy of the Declaration will be submitted to the Examiner shortly.

Applicants Need to Disclose Only What is Disclosed in the Cited Reference to Support the Priority Claim

Applicants respectfully submit that in order to overcome the 35 U.S.C. §102(e) rejection over Holtzman *et al.*, the Declaration by Dr. Desnoyers, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood ("Declaration") simply needs to provide a disclosure commensurate in scope with the disclosure in the prior art document by Holtzman *et al.* to support the priority claim.

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel, 241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single

species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 37 C.F.R. §1.131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the Court stated in support of its decision that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. §1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, **an applicant need only show that portion of his or her claimed invention that appears in the cited reference**.

As the Examiner noted, Holtzman *et al.* discloses a nucleic acid encoding a polypeptide (human A236 protein) that is 100% identical to SEQ ID NO:59. Holtzman *et al.* discloses that human A236 shares homology to CAR. Although Holtzman *et al.* includes general statements regarding possible uses of the sequence, no specific examples or experimental data are provided regarding the use of human A236.

Applicants respectfully submit that since Holtzman *et al.* only disclose a polypeptide sequence, its encoding nucleic acid sequence, and a sequence homology, without any disclosure to support utility, the Declaration simply needs to show possession of the polypeptide sequence and its encoding polynucleotide sequence as well as a sequence homology, as disclosed in Holtzman *et al.,* in order to remove the reference as prior art under 35 U.S.C. §102.

Applicants respectfully submit that U.S. Provisional Application Serial No. 60/078,910 filed on March 20, 1998, provides the nucleic acid and amino acid sequences of the PRO363 polypeptide.

The Declaration clearly states that U.S. Provisional Application Serial No. 60/078,910 filed on March 20, 1998 discloses sequences designated as SEQ ID NO:1 and SEQ ID NO:3, which are identical to SEQ ID NO:58 and SEQ ID NO:59, respectively, of the above-identified application. U.S. Provisional Application Serial No. 60/078,910 further discloses that the full length PRO363 polypeptide (SEQ ID NO:59) has significant homology to the cell surface protein HCAR.

Accordingly, Applicants respectfully submit that the disclosures are commensurate in scope and that U.S. Provisional Application Serial No. 60/078,910 discloses all that the cited prior art discloses.

Consequently, based on the holdings of *In re* Stempel and *In re* Moore, Holtzman *et al.* is not prior art under §102 since its effective priority date is <u>after</u> the invention by the Applicants for patent.

Accordingly, withdrawal of the rejection of Claim 58-64, 66, 68-70, and 74-77 under 35 U.S.C. §102(e) as anticipated by Holtzman *et al.* is respectfully requested.

VIII. <u>Claim Rejections Under 35 U.S.C. §103</u>

Claims 63, 65 and 67 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Holtzman *et al.* Holtzman *et al.* discloses an isolated nucleic acid that encodes

a polypeptide, human A236 protein, that is 100% identical to SEQ ID NO:59, as well as expression vectors and host cells comprising the nucleic acid. The Examiner asserts that because Holtzman *et al.* discloses the structural domains of human A236 protein, including the signal peptide and the extracellular domain, it would have been obvious to one of ordinary skill in the art to make nucleic acids encoding the A236 protein lacking its signal peptide, or the extracellular domain of the A236 protein.

Applicants submit that, as discussed above, Holtzman *et al.* is not prior art under §102 since its effective priority date is after the invention by the Applicants for patent. As such, Holtzman *et al.* is not a proper reference under any section of 35 U.S.C. §102. Therefore, Holtzman *et al.* is not available to support a rejection under 35 U.S.C. §103.

Accordingly, withdrawal of the rejection of Claims 63, 65 and 67 under 35 U.S.C. §103(a) over Holtzman *et al.* is respectfully requested.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C72**).

Respectfully submitted,

Date: October 5, 2005

By: _____
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